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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/524,081	02/24/2006	Anita Mehta	RLL -260US	4225
26815	7590	06/21/2007	EXAMINER	
RANBAXY INC. 600 COLLEGE ROAD EAST SUITE 2100 PRINCETON, NJ 08540			NOLAN, JASON MICHAEL	
			ART UNIT	PAPER NUMBER
			1626	
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			06/21/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/524,081

Applicant(s)

MEHTA ET AL.

Examiner

Jason M. Nolan, Ph.D.

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 24 February 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-12 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1 and 4-8 is/are rejected.
- 7) ☒ Claim(s) 2,3 and 9-12 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>02/24/2006</u> . | 6) <input type="checkbox"/> Other: _____ |

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DETAILED ACTION

Claims 1-12 are pending in the instant application.

Oath/Declaration

The oath is objected to because it was not executed in accordance with either 37 CFR 1.66 or 1.68. Specifically, one applicant, Anita Mehta, has not executed the oath.

Information Disclosure Statement

Applicants' information disclosure statement (IDS), filed on 02/24/2006 has been considered. Please refer to Applicants' copy of the 1449 submitted herein.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 4 & 8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the compounds of the formula I; including enantiomers, diastereomers, N-oxides and pharmaceutically acceptable salts thereof; the specification is not enabled for *solvates, esters, polymorphs, prodrugs or metabolites* thereof. The specification does not enable any person skilled in the art to

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which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The Nature of the Invention

The nature of the invention is the compounds of formula I, and all pharmaceutically acceptable salts, pharmaceutically acceptable solvates, esters, enantiomers, diastereomers, N-oxides, polymorphs, prodrugs or metabolites thereof.

The state of the prior art and the predictability or lack thereof in the art

Active pharmaceutical ingredients (APIs) are frequently delivered to the patient in the solid-state as part of an approved dosage form (e.g., tablets, capsules, etc.). Solids provide a convenient, compact and generally stable format to store an API or a drug product. Understanding and controlling the solid-state chemistry of APIs, both as pure drug substances and in formulated products, is therefore an important aspect of the drug development process. APIs can exist in a variety of distinct solid forms, including polymorphs, solvates, hydrates, salts, co-crystals and amorphous solids. Each form displays unique physicochemical properties that can profoundly influence the bioavailability, manufacturability purification, stability and other performance characteristics of the drug. Hence, it is critical to understand the relationship between the particular solid form of a compound and its functional properties.

For ionizable compounds, preparation of salt forms using pharmaceutically acceptable acids and bases is a common strategy to improve bioavailability. However,

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the preparation of other solid forms such as polymorphs and solvates are not so common as to be predictable. In order to obtain patent protection on these forms, some of which may have significantly different properties and relevance as development candidates, it is essential to prepare them, identify conditions for making them and evaluate their properties as valuable new pharmaceutical materials. A large number of factors can influence crystal nucleation and growth during this process, including the composition of the crystallization medium and the processes used to generate supersaturation and promote crystallization, (Morissette *et al.* Advanced Drug Delivery Reviews **2004**, 56, 275-300).

For instance, the phenomenon of polymorphism, in the crystallization of organic compounds, is of crucial importance to the pharmaceutical industry. Two polymorphs of the same drug molecule may have different physical properties: e.g. solubility, bioavailability, melting points, density, hardness, or color; and may have dramatically different properties that effect the scale-up process. Due to the differences between polymorphs, the drug regulatory authorities (e.g. the FDA) are increasingly demanding more information about potential drug products before granting approval. The conditions under which polymorphs interconvert is also of crucial importance, particularly when drugs may encounter exposure to changes in temperature, pressure, and relative humidity during processes such as drying, granulation, milling, compression, and storage. Therefore, for these reasons, the state of the prior art is one of unpredictability. The science of crystallization has evolved such that said differences in properties implies patentable distinctiveness between polymorphs.

Amount of direction/guidance & presence or absence of working examples

There is guidance for the preparation of the compounds in the specification (pages 6-14); however, no direction or guidance is present in the instant specification for the preparation of solvates, esters, polymorphs, prodrugs, and metabolites for the compounds of formula I. Also, there are no working examples present in the disclosure for solvates, esters, polymorphs, prodrugs, and metabolites for the compounds of formula I. Therefore, one of skill in the art would be required to identify the correct solvent system and crystallization technique for each compound and, further, identify the similarities and differences between crystals and corresponding spectral data for each compound (polymorph) in order to determine what is being claimed.

The breadth of the claims

The instant breadth of the rejected claims is broader than the disclosure, specifically; the instant claims include compounds of formula I, and all pharmaceutically acceptable salts, pharmaceutically acceptable solvates, esters, enantiomers, diastereomers, N-oxides, polymorphs, prodrugs or metabolites thereof.

The quantity of experimentation necessary

While the level of the skill in the pharmaceutical arts is high, it would require undue experimentation of one of ordinary skill in the art to prepare any solvates, esters, polymorphs, prodrugs or metabolites of a compound according to formula I as instantly claimed. The science of crystallization has evolved such that, without guidance or

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working examples for polymorphs in the specification, the claims lack enablement. This rejection can be overcome by deletion of the words: solvates, esters, polymorphs, prodrugs, and metabolites from **Claims 1, 4 & 8**.

Claims 4-7 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while enabling for compositions and a method of *treatment* for some diseases or disorders of the respiratory, urinary and gastrointestinal systems, (such as those listed in **Claim 5**: urinary incontinence, lower urinary tract symptoms (LUTS), bronchial asthma, chronic obstructive pulmonary disorders (COPD), pulmonary fibrosis, irritable bowel syndrome, obesity, diabetes and gastrointestinal hyperkinesis), it does not reasonably provide enablement *for the treatment or for the prophylaxis* for any diseases or disorders of the respiratory, urinary and gastrointestinal systems. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The nature of the invention

The nature of the invention is compounds and compositions of formula I, the process for preparing these compounds, and methods of using these compounds.

The state of the prior art and the predictability or lack thereof in the art

The state of the prior art, namely pharmacological art, involves screening *in vitro* and *in vivo* to determine if the compounds exhibit desired pharmacological activities, which are then tested for their efficacy on human beings. There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face. The instant claimed invention is highly unpredictable as discussed below.

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In the instant case, the claimed invention is highly unpredictable since one skilled in the art would recognize that a group of compounds and compositions may provide a treatment for conditions such as urinary incontinence, lower urinary tract symptoms (LUTS), bronchial asthma, chronic obstructive pulmonary disorders (COPD), pulmonary fibrosis, irritable bowel syndrome, obesity, diabetes and gastrointestinal hyperkinesis, but it does not mean that the same group of compounds and compositions may prevent said conditions.

***The amount of direction or guidance present and the presence or absence of
working examples***

There is no direction or guidance provided which supports Applicant's claimed method for the prophylaxis of diseases or disorders of the respiratory, urinary and gastrointestinal systems as indicated. The direction or guidance present in Applicants' Specification for a method of using the compounds and compositions of formula I to treat clinical conditions such as urinary incontinence, lower urinary tract symptoms (LUTS), bronchial asthma, chronic obstructive pulmonary disorders (COPD), pulmonary fibrosis, irritable bowel syndrome, obesity, diabetes and gastrointestinal hyperkinesis is found on pages 14-16.

The breadth of the claims, quantity of experimentation, and level of skill in the art

Claims 4-7 are drawn to "the treatment or prophylaxis ..." Prophylaxis is commonly known to be synonymous with prevention. In order to prevent a disease, one would need to precisely identify those subjects likely to acquire such a disease, administer Applicant's claimed invention, and then demonstrate that if the identified subject did not develop the disease, such an effect was the direct result of administration of the claimed invention.

Because of the aforementioned reasons, a person of skill in the art could not practice the claimed invention herein, or a person of skill in the art could practice the claimed invention herein only with undue experimentation and with no assurance of

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success. Deleting the word "prophylaxis" in **Claims 4 & 6** and incorporating the limitations of **Claims 5 & 7** into **Claims 4 & 6** can overcome this rejection.

Allowable Subject Matter

The present invention pertains to the 3-azabicyclo[3.1.0]hexane derivatives according to formula I and methods of using these compounds for the treatment of muscarinic receptor related disorders. The compounds according to formula I are free of the prior art; nothing known in the art anticipates or renders the compounds of the instant application obvious. The closest prior art is the compound B11 (see column 52) in US Patent 6,191,165 by Ognyanov *et al.* The instant case is distinguished from said compound because that compound has unsubstituted phenyl rings; whereas the compounds according to formula I contains a methyl and an oxygen containing substituent on one of the phenyl rings.

One skilled in the art would be enabled to make and use the compounds taught herein for the treatment of muscarinic receptor related disorders (such as those listed in Claim 5) using the teachings of the Specification in conjunction with the teachings in the prior art.

Claim Objections

Claim 2 is objected to because of the following informalities: the list should include the word "and" between the last two species. Appropriate correction is required.

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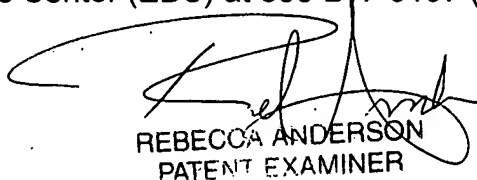
Claims 3 & 9-12 are objected to as being dependent upon a rejected base, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Telephone Inquiry

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jason M. Nolan, Ph.D.** whose telephone number is **(571) 272-4356** and electronic mail is **Jason.Nolan@uspto.gov**. The examiner can normally be reached on Mon - Fri (9:00 - 5:30PM). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joseph M^cKane** can be reached on **(571) 272-0699**. The fax phone number for the organization where this application or proceeding is assigned is **571-273-8300**. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Jason M. Nolan, Ph.D.
Examiner
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REBECCA ANDERSON
PATENT EXAMINER

for Joseph K. M^cKane
Supervisory Patent Examiner
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Date: June 17, 2007